REMARKS

In response to the Office Action dated November 17, 2008, Applicant has amended claims 1, 2 and 14 to solely clarify particular aspects of the invention. Claims 13, 15, 25, and 26 have been canceled and no new claims have been added. Support for all the above amendments may be found throughout the specification as originally filed, for example, at page 6, lines 30-31, page 7, lines 25-26; and original claim 15. No new matter has been added. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendments, 1-12, 14, 16-18, and 27-28 are under pending and under examination.

A telephonic interview on April 1, 2009, was conducted and attended by Examiner Karen Canella and Dr. William Christiansen (Reg. No. 44,614). During the interview, the Examiner kindly suggested that providing additional examples of antibodies and antigens that could be used to target cells of a vascular lesion would be useful to establish the enablement of the presently claimed invention. Neither exhibits nor demonstrations were used during the interview.

Applicant thanks the Examiner for her suggestions, and provides herewith, additional examples of antibodies and antigens useful for targeting cells of a vascular lesion.

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Applicant respectfully submits that the claim 1 has been amended, without acquiescence, to recite, a method comprising a ligand that selectively binds to ~~a receptor~~an antigen on the target cells of the lesion in the vascular system, wherein the ligand is an antibody or an antibody fragment specific to the antigen selected from the group consisting of tumor surface antigen; tumor endothelial antigen; non-tumor endothelial antigen; tumor vessel wall antigen; neointimal antigens; arterial plaque antigens; and vascular smooth muscle cell antigens.

The as-filed specification clearly teaches the presently claimed antigens (for example, see page 6, lines 30-31) and that one type of suitable ligand-receptor binding pair is an antigen-antibody binding pair (for example, see page 8, line 6). Thus, this amendment does not contain new matter.

Applicant further submits that the claim 2 has been amended, without acquiescence, to recite, a method comprising a first member of a ligand-receptor binding pair conjugated to an antibody or antibody fragment, wherein the antibody or antibody fragment selectively binds to an antigen on the target cells ~~that comprises~~of the lesion in the arterial vascular system, wherein said antigen selected from the group consisting of tumor surface antigen; tumor endothelial antigen; non-tumor endothelial antigen; tumor vessel wall antigen; neointimal antigens; arterial plaque antigens; and vascular smooth muscle cell antigens. The as-filed specification clearly teaches that suitable antigens targeted on vascular lesions included the presently claimed antigens (for example, see page 7, lines 25-26 and original claim 15). Thus, this amendment does not contain new matter.

Withdrawn Claims

The Examiner contends that claims 13, 14, and 26 are erroneously identified as withdrawn. Applicant, without acquiescence, has canceled claims 13 and 26 and has amended the status identifier of claim 14 to "Original". Applicant respectfully submits that the status identifiers of all claims are now correct.

Claims Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 2-18 and 27-28 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner contends that claim 2 is vague because it is unclear how the target cell can "comprise" the lesion itself, since the lesion is multi-cellular. Therefore, the Examiner suggests that amending claim 2 to recite "target cells of the lesion" would overcome this rejection.

Applicant kindly thanks the Examiner for suggesting claim language to obviate this basis of rejection.

Thus, Applicant, without acquiescence and solely in a good faith effort to expedite prosecution, has amended claims 1 and 2 to recite "target cells of the lesion" as suggested by the Examiner; thus, obviating this basis for rejection. Reconsideration and withdrawal of this basis for rejection is respectfully requested.

Claims Rejection Under 35 U.S.C. §112, First Paragraph, Enablement

Claims 1-18 and 25-28 stand rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Specifically, the Examiner alleges that while the specification enables methods relying on antibodies which selectively bind to epitopes which are part of a vascularized tumor, it does not reasonably provide enablement for methods relying on the direct binding of heparin, angiotensin II, LDL, or VLDL to receptors of the vascular lesion.

Applicant respectfully traverses this basis for rejection and submits that the as-filed specification fully enables the presently claimed invention. Moreover, Applicant submits that the skilled artisan would not be subjected to undue experimentation in order to practice the entire breadth of presently claimed invention.

Applicant kindly thanks the Examiner for acknowledging that the as-filed specification enables methods relying on antibodies which selectively bind to epitopes which are part of a vascularized tumor and that antibodies can be used to specifically target diagnostic or therapeutic agents *in vivo*, to specific sites via antigen-antibody interactions which are specific to the targeted tissues. The Examiner contends that both independent claims 1 and 2 require a specific binding agent for a vascular lesion, wherein said agent can be therapeutically effective when administered *in vivo*.

The Examiner further contends that the specification does not describe any of the antibodies or the specific antigen or epitopes that are being targeted and that the prior art provides examples of antibodies that successfully target atherosclerotic plaques or blood clots.

However, the Examiner concludes that the description of only a few antibodies in the prior art, which have the ability to distinguish plaques or blood clots from normal vessel walls and blood clots does not reasonably provide enablement for the broad requirement of an antibody which specifically binds to targeted lesions of the vascular system before the claimed method of treatment can be carried out. Applicant respectfully disagrees.

Applicant respectfully submit that the Examiner rightly contends that Tsimikas et al. (WO98/21581) and Ditlow et al. (U.S. Patent No. 5,811,248) teach antibodies that specifically target atherosclerotic plaques and that Matsueda et al. (WO87/06263) teach antibodies to cross-linked fibrin, which was shown to be sufficient for targeting heparin to sites of restenosis (Thomas *et al.*, Journal of Controlled Release, 2004, Vol. 100, pp. 357-377; of record). In view of the foregoing Examples provided by the Examiner, the level of skill in the art, and the guidance provided by the as-filed specification, the as-filed specification clearly enables one having ordinary skill in the art how to make and use antibodies that target a conjugated photosensistizing agent to a vascular lesion.

The written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof.). "[A] disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation).

Moreover, Applicant submits that further antigens and antibodies that specifically target lesions of the vascular system were known in the art at the time the instant application was filed; further demonstrating enablement with regarding to using antibodies to specifically target lesions of the vascular system.

For example, with regard to antigens and antibodies suitable to target a therapeutic to a vascular lesion, Tsimikas et al., *Radiolabeled MDA2, an oxidation-specific, monoclonal antibody, identifies native atherosclerotic lesions in vivo.* J Nucl Cardiol. 1999 Jan-Feb;6(1 Pt 1):41-53, teach monoclonal antibodies that specifically identify atherosclerotic lesions; Carrió et al., *Noninvasive localization of human atherosclerotic lesions with indium 111-labeled monoclonal Z2D3 antibody specific for proliferating smooth muscle cells.* J Nucl Cardiol. 1998 Nov-Dec;5(6):551-7, teach that Z2D3 antibody is specific to profilerating smooth muscle cells, which are localized to many types of vascular lesions; Praticò et al., *Localization of distinct F2-isoprostanes in human atherosclerotic lesions.* J Clin Invest. 1997 Oct 15;100(8):2028-34 teach that the isoprostanes, 8-epi PGF2alpha and IPF2alpha-I, are localized to atherosclerotic lesions; O'Brien et al., *Vascular cell adhesion molecule-1 is expressed in human coronary atherosclerotic plaques. Implications for the mode of progression of advanced coronary atherosclerosis.* J Clin Invest. 1993 Aug;92(2):945-51, teach that VCAM-1 is more prevalent in diseased vasculature comprising atherosclerotic plaques compared to vasculature without plaque; Desmoulière et al. *Phenotypic expression of surface antigens of rabbit aortic smooth muscle cells in culture. Monoclonal antibody, 2P1A2, characteristic of smooth muscle cells present in atherosclerotic plaque, is not correlated with cell proliferation.* Atherosclerosis. 1990 Nov;85(1):25-35, teach a monoclonal antibody to specifically target vascular smooth muscle cells present at sites of vascular lesions; Rogers et al. *A mAb to the beta2-leukocyte integrin Mac-1(CD11b/CD18) reduces intimal thickening after angioplasty or stent implantation in rabbits.* Proc Natl Acad Sci U S A. 1998 Aug 18;95(17):10134-9, teach that monoclonal antibodies can be used to target vascular lesions; Bosmans et al. *Fibrin(ogen) and von Willebrand factor deposition are associated with intimal thickening after balloon angioplasty of the rabbit carotid artery.* Arterioscler Thromb Vasc Biol. 1997 Apr;17(4):634-45, teach that Fibrin(ogen) and von Willebrand factor are antigens that are specifically upregulated at vascular lesions; Chen et al., *Overexpression of human endothelial nitric oxide synthase in rat vascular smooth muscle cells and in balloon-injured carotid artery.* Circ Res. 1998 May 4;82(8):862-70 teach that nitric oxide synthase is upregulated in vascular smooth muscle cells present at vascular lesions; and Chinnaswamy et al. *Gp60 Activation Mediates Albumin transcytosis in endothelial*

cells by tyrosine kinase dependent pathway. JBC 1997, pp.25968-25975, teach the endothelial cell specific antigen Gp60 and antibodies effective in targeting the antigen. Endothelial cells are present in the intimal layer of the vasculature and have a role in neointimal thickening.

Applicant respectfully points out that the Examiner has not considered the claims as a whole, but instead, has focused only on a particular aspect of the claim. The claims require local irradiation of the subject. Thus, only those areas wherein the antibody has localized the photosensitizing conjugate to the vascular leasion **and** that are directly exposed to the radiation will activate the photosensitizing agent and elicit PDT. Other non-target tissues in the subject would be spared of the activated photosensitizing agent, whether bound by antibody or not.

Furthermore, it is a common practice in treating vascular lesions to occlude blood flow away from the area of the lesion with catheter balloons or pressure cuffs; thus, localizing the targeting agent to the area of the vascular lesion, which further spares other non-target tissues in the subject from receiving the photosensitizing agent.

Thus, a skilled artisan can practice the presently claimed invention by using one of the many existing antibodies to cells of a vascular lesion described in the art and by developing antibodies specific to known antigens of cells of a vascular lesion. The skilled artisan would not be required to engage in undue experimentation, as the methods of antibody conjugation, protein purification, and antibody generation are all well known and routine methods used in the art. Furthermore, the activation of the photosensitizing agent is a local event, i.e., activation only occurs at the vascular lesion where the subject has been irradiated. Thus, although the experimentation may be complex, routine experimentation that is complex, is not undue.

The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation

should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989).

The Examiner further contends that claims 13 and 26, now canceled, encompass ligands which are LDL, VLDL, heparin or angiotensin II, which would not be specific for the targeting of the instant photosensitizing agents to a vascular lesion. Applicant respectfully submits that the presently amended claims are drawn to targeting agents comprising antibodies in order to target the PDT therapeutic to a vascular lesion. Thus, the Examiner's argues with regard to the lack of specific binding of biotin/streptavidin, a chemokine, a growth factor, LDL, VLDL, heparin, and angiotensin II to vascular lesions are now moot.

Accordingly, in view of the instant disclosure, Applicant submits that the as-filed specification fully enables one of ordinary skill in the art to practice the presently claimed invention without undue experimentation. Reconsideration and withdrawal of this basis of rejection is respectfully requested.

Claims Rejection Under 35 U.S.C. §112, First Paragraph, Written Description

Claims 1-18 and 25-28 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges that the claims contain subject matter which was not described in such a way as to reasonably convey to the skilled artisan that the Applicant was in possession of the claimed invention at the time of filing the instant application.

Applicant respectfully traverses this basis for rejection and submits that the as-filed specification provides full written description support for the entire breadth of the presently claimed invention. Furthermore, one having ordinary skill in the art would reasonably conclude that Applicant was in possession of the presently claimed invention at the time of filing the instant application.

The Examiner contends that the instant claims require ligands or antibodies which specifically bind to target cells within vascular lesions that include arterial plaques and that the ligand can be an antibody which specifically binds to neointimas, arterial plaques, vascular smooth muscle cells and/or the abnormal cellular matrix of the site to be treated. The Examiner further contends that the specification lacks a description of such antibodies or a description of the complete protein or carbohydrate structure to which said antibodies specifically bind. Therefore, the Examiner concludes that although the art describes three examples of antibodies that can be used to target cells of vascular lesions, only three antibodies is not a satisfactory description of a genus of antibodies which can specifically bind to a vascular lesion because said lesion is complex including multiple cell types and products produced therefrom. Applicant respectfully disagrees.

Applicant submits that the complexity of the lesion is not necessarily critical, given that the photosensitizing therapeutic can be delivered to the vascular lesion by targeting any given cell type present at the lesion. Thus, a vascular lesion comprising proliferating neointimal cells, vascular smooth muscle cells, or atherosclerotic plaques can effective be targeted by an antibody that recognizes antigens for any of the cells or plaques present at the lesion.

As noted above, in response to the enablement rejection, Applicant has provided numerous examples of existing antigens and antibodies that are suitable to a photosensitizing agent to target cells of a vascular lesion. Thus, in view of the numerous examples above, the skill in the art, and the guidance presented in the as-filed specification, the skilled artisan would reasonably conclude that Applicant was in possession of the presently claimed invention at the time the instant application was filed.

Reconsideration and withdrawal of this basis of rejection is respectfully requested.

Applicant respectfully submits that all of the claims remaining in the application are now believed to be in condition for allowance. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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